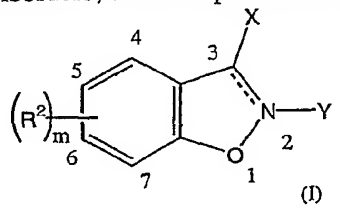
Claims

1. The use of a DAAO inhibiting compound for the manufacture of a medicament for the treatment of mental disorders, said compound having the formula



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer from 1 to 3;

X represents hydroxy, amino, –oxo or –Z-R^1;

Y is absent or represents –(C=O)-R^6;

Z represents carbonyl, -oxy-carbonyl-, =N-carbonyl- or -NR^5-carbonyl;

R^1 represents hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxy-, Ar^1, Ar^2-C_{1-4}alkyl-, -NR^3R^4 or -Het^1;

R^2 represents hydrogen, halo, hydroxy, nitro, cyano, hydroxycarbonyl-, amino, mono- or di (C_{1-4}alkyl)amino-, C_{1-6}alkyloxycarbonyl-, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy-, C_{1-4}alkyloxy- optionally substituted with one or more halo atoms or R^2 represents C_{1-4}alkyl optionally substituted with one or more halogen atoms;

R^3 and R^4 are each independently selected from hydrogen, Het^2, Ar^3, C_{1-4}alkyl or C_{1-4}alkyl substituted with one or more substituents selected from halo, hydroxy or C_{1-4}alkyloxy-;

R^5 represents hydrogen, C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl- or Ar^4-carbonyl-;

R^6 represents a substituent selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy-, Ar^5, Ar^6-C_{1-4}alkyl-, -NR^7R^8 or Het^3;

R^7 and R^8 are each independently selected from hydrogen, Het^4, Ar^7, C_{1-4}alkyl or C_{1-4}alkyl substituted with one or more substituents selected from halo, hydroxy or C_{1-4}alkyloxy-;

Het^1 represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of

amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Het ^{2} represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Het ^{3} represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Het^4 represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Ar^1, Ar^2, Ar^3, Ar^4, Ar^5, Ar^6 or Ar^7 each independently represents phenyl optionally substituted one or where possible two or more substituents selected from halo, nitro, C_{1-4}alkyl, hydroxy or C_{1-4}alkyloxy-.

2. The use according to claim 1 wherein for the compounds of formula (I)

m represents an integer from 1 to 3;

X represents –oxo or $-Z-R^1$;

Y is absent when X represents $-Z-R^1$ and $-(C=O)-R^6$ when X represents oxo;

Z represents carbonyl, -oxy-carbonyl- or $-NR^5$-carbonyl-;

R^1 represents C_{1-4}alkyl, Ar^1, Ar^1-C_{1-4}alkyl-, $-NR^3R^4$ or $-Het^1$;

R^2 represents hydrogen, halo, nitro, hydroxycarbonyl-, C_{1-4}alkyloxy or C_{1-4}alkyl;

R^3 and R^4 are each independently selected from hydrogen, Ar^3 or C_{1-4}alkyl;

R^5 represents hydrogen, C_{1-4}alkylcarbonyl- or Ar^4-carbonyl-;

R^6 represents a substituent selected from the group consisting of C_{1-4}alkyl, Ar^5, Ar^6-C_{1-4}alkyl- or NR^7R^8;

R^7 and R^8 are each independently selected from hydrogen, Het^4 or C_{1-4}alkyl;

Het^1 represents a heterocycle selected from oxazolyl, isoxazolyl, imidazolyl or pyrazolyl wherein said heterocycle is optionally substituted with one, two or three substituents selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents, in particular said heterocycle is substituted with one or more substituents selected from the group consisting of C_{1-4}alkyl, phenyl or phenyl substituted with one or more halo substituents; in a particular embodiment Het^1 represents a heterocycle selected from isoxazolyl and pyrazolyl wherein said heterocycle is substituted with one or more substituents selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents, in particular said heterocycle is substituted with one or more substituents selected from the group consisting of C_{1-4}alkyl, phenyl or phenyl substituted with one or more halo substituents;

Het^4 represents a heterocycle selected from oxazolyl or isoxazolyl, wherein said heterocycle is optionally substituted with one or more substituents selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl and phenyl substituted with one or more halo substituents, in particular said heterocycle is substituted with one or more substituents selected from C_{1-4}alkyl, phenyl or phenyl substituted with one or more halo substituents; in a particular embodiment Het^4 represents isoxazolyl substituted with one or more substituents selected from C_{1-4}alkyl, phenyl or phenyl substituted with one or more halo substituents;

Ar^1, Ar^2, Ar^3, Ar^4, Ar^5 or Ar^6 each independently represents phenyl;

3. A compound of formula (I) a defined in claims 1 or 2, provided however that when;

- Z is -oxycarbonyl and R^1 is chloro- or nitro-phenyl-, then R^2 <u>is not</u> methyloxy-, ethyloxy-, chloro or fluoro,
- Z is -oxycarbonyl and R^1 is methyl, methyloxy-, ethyloxy-, phenyl, chlorophenyl, nitrophenyl, isoxazolyl substituted with chloro or methyl or when R^1 is pyrazolyl substituted with ethyl and methyl, then R^2 <u>is not</u> hydrogen, chloro, fluoro, bromo, ethyloxy, methyloxy or methyl,
- Z is -NR^5-carbonyl and R^1 is methyl, methyloxy-, ethyloxy-, t-butyloxy-, benzyloxy-, phenyl or di-chlorophenyl, then R^2 <u>is not</u> hydrogen, halo, methyl or trifluoromethyl, or

- Z is oxycarbonyl and R^3 or R^4 is a methyl, isopropyl, propyl, t-butyl or an isoxazolyl substituted with either chloro, one methyl substituent or with one methyl and one di-chloro-phenyl substituent, then R^2 is not hydrogen, chloro or methyl.

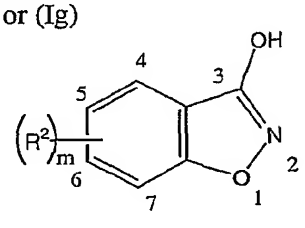
4. A compound of formula (I) wherein R^1 is a heterocycle Het^1 selected from the group consisting of isoxazolyl, pyrazolyl or benzisoxazolyl wherein said Het^1 is optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-4}alkyl, phenyl and phenyl substituted with one or more halo substituents,
provided that when R^1 is a substituted isoxazolyl or a substituted pyrazolyl, then R^2 is not hydrogen, chloro or methyl.

5. A compound of formula (I) as claimed in claims 3 or 4, for use as a medicine.

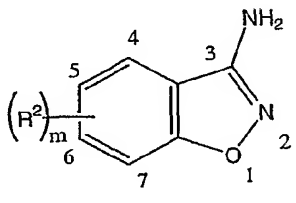
6. Use of a compound of formula (I) as claimed in any of claims 1 to 4 in the manufacture of a medicament for the treatment of schizophrenia.

7. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I).

8. The use of intermediates with DAAO inhibiting activity in the manufacture of a medicament for treatment of mental disorders, said intermediates having formula (Ia) or (Ig)



(Ia)



(Ig)

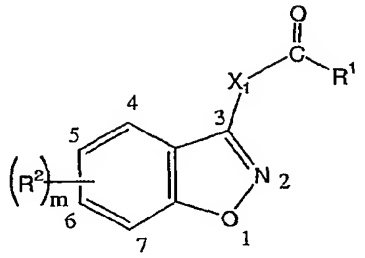
the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer from 1 to 3;

R^2 represents hydrogen, halo, hydroxy, nitro, cyano, hydroxycarbonyl-, amino, mono- or di (C_{1-4}alkyl)amino-, C_{1-6}alkyloxycarbonyl-, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy-, C_{1-4}alkyloxy- optionally substituted with

one or more halo atoms or R^2 represents C_{1-4}alkyl optionally substituted with one or more halogen atoms.

9. A compound of formula



(Ic)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer from 1 to 3;

X_1 represents O or NR^5;

R^1 represents C_{1-4}alkyl, C_{1-4}alkyloxy-, Ar^1, Ar^2-C_{1-4}alkyl-, -NR^3R^4 or Het^1;

R^2 represents hydrogen, halo, hydroxy, nitro, hydroxycarbonyl-, amino, mono- or di (C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl-, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy-, C_{1-4}alkyloxy- optionally substituted with one or more halo atoms or R^2 represents C_{1-4}alkyl optionally substituted with one or more halogen atoms;

R^3 and R^4 are each independently selected from hydrogen, Het^2, phenyl, C_{1-4}alkyl or C_{1-4}alkyl substituted with one or more substituents selected from halo, hydroxyl, phenyl or C_{1-4}alkyloxy-;

R^5 represents hydrogen, C_{1-4}alkyl, phenyl-carbonyl- or C_{1-4}alkyl-carbonyl-;

Het^1 represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Het^2 represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of

amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents,

provided that when;

- X_1 is -O- and R^1 is methyl, methyloxy-, ethyloxy-, phenyl, chlorophenyl, nitrophenyl, isoxazolyl substituted with chloro or methyl or when R^1 is pyrazolyl substituted with ethyl and methyl, then R^2 is not hydrogen, chloro, fluoro, bromo or methyl,
- X_1 is NR^5 and R^1 is methyl, methyloxy-, ethyloxy-, t-butyloxy-, benzyloxy-, phenyl or di-chloro-phenyl, then R^2 is not hydrogen, halo, methyl or trifluoromethyl,
- X_1 is -O- and R^3 or R^4 is a methyl, isopropyl, propyl, t-butyl or an isoxazolyl substituted with either chloro, one methyl substituent or with one methyl and one di-chloro-phenyl substituent, then R^2 is not hydrogen, chloro or methyl.

10. A compound according to claim 9 wherein

m is 1;

X_1 represents O or NR^5;

R^1 is NR^3R^4 or Het^1;

R^2 is hydrogen, halo or R^2 represents C_{1-4}alkyl;

R^3 and R^4 are each independently selected from hydrogen, Het^2 and C_{1-4}alkyl;

R^5 represents hydrogen or C_{1-4}alkyl-carbonyl-;

Het^1 is isoxazolyl or imidazolyl each independently substituted with one or more substituents selected from C_{1-4}alkyl and phenyl substituted with one or more halo substituents;

Het^2 is isoxazolyl substituted with one or more substituents selected from C_{1-4}alkyl and phenyl substituted with one or more halo substituents.

11. A compound according to claim 9 wherein

m is 1;

X_1 represents NR^5;

R^1 is NR^3R^4 or Het^1;

R^2 is hydrogen, chloro or methyl;

R^3 represents hydrogen and R^4 is C_{1-4}alkyl, phenyl or C_{1-4}alkyl substituted with phenyl;

R^5 represents hydrogen, phenyl-carbonyl- or C_{1-4}alkyl-carbonyl-;

Het^1 is isoxazolyl or imidazolyl each independently substituted with one or more substituents selected from C_{1-4}alkyl and phenyl substituted with one or more halo substituents;

Het^2 is isoxazolyl substituted with one or more substituents selected from C_{1-4}alkyl and phenyl substituted with one or more halo substituents.

12. A compound according to claim 9 wherein X_1 represents O and R^3 and R^4 are each independently selected from Het^2, Ar^3, C_{1-4}alkyl or C_{1-4}alkyl substituted with one or more substituents selected from halo, hydroxy or C_{1-4}alkyloxy-.

13. A compound according to any of claims 9 to 12 for use as a medicine.

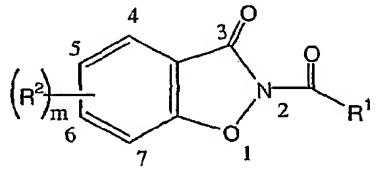
14. Use of a compound of formula (Ic) in the manufacture of a medicament for treating mental disorders such as schizophrenia.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective DAAO inhibitory amount of a compound as described in any one of the claims 3, 4 or 9 to 12.

16. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I).

17. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of an intermediate of formula (Ia) or (Ig).

18. A compound of formula



(Id)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer from 0 to 3;

R^1 represents hydrogen, C_{1-4}alkyl, C_{1-4}alkyloxy, Ar^1, Ar^2-C_{1-4}alkyl, NR^3R^4 or Het^1;

R^2 represents hydrogen, halo, hydroxy, nitro, cyano, hydroxycarbonyl-, amino, mono- or di (C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl-, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy-, C_{1-4}alkyloxy- optionally substituted with one or more halo atoms or R^2 represents C_{1-4}alkyl- optionally substituted with one or more halogen atoms;

R^3 and R^4 are each independently selected from hydrogen, Het^2, Ar^3, C_{1-4}alkyl or C_{1-4}alkyl substituted with one or more substituents selected from halo, hydroxy or C_{1-4}alkyloxy-;

Het^1 represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said Het^1 is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Het^2 represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said Het^1 is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl- and phenyl substituted with one or more halo substituents;

Ar^1, Ar^2 or Ar^3 each independently represents phenyl optionally substituted one or where possible two or more substituents selected from halo, nitro, C_{1-4}alkyl, hydroxy or C_{1-4}alkyloxy.

provided that when;

- m represents 1 and R^1 represents chloro- or nitro-phenyl, then R^2 is not hydrogen, methoxy, ethoxy, chloro or fluoro;
- R^1 represents ethoxy or methoxy, then R^2 is not hydrogen, bromo, fluoro or chloro;
- R^1 represents methyl, then R^2 is not hydrogen, bromo or chloro.

19. A compound of formula (Id) for use as a medicine.

20. Use of a compound of formula (Id) in the manufacture of a medicament for treating mental disorders such as schizophrenia.

21. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of an intermediate of formula (Id).

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